Review

Possible role of vitamin D_3 on the adipocyte/fibroblast trans-differentiation mediated by pancreas cancer

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ABSTRACT: In pancreatic tumors, white adipose tissue and metabolic disorders related to adipocytes, are recently reviewed as important co-factors in pancreas pathology. Cell differentiation in pancreatic cancer might involve therefore adipose tissue and factors released by adipocytes should play a fundamental role both in cancer onset and in its progression. Among these molecules, a great interest has been devoted quite recently to the hormonal role exerted by vitamin D_3 in pancreatic cancer, particularly its active 1,25 dihydroxylated form. Despite the wide bulk of evidence reporting the chemopreventive role of vitamin D, the mechanism by which active vitamin D_3 is able to counteract cancer progression and malignancy is yet far to be elucidated.

KEYWORDS: *vitamin D3, adipocyte, pancreas cancer*

Introduction

Cancer is a very complex pathology where epithelial/mesenchymal transition (EMT) should play a major role [1]. In pancreatic tumors, white adipose tissue and metabolic disorders related to adipocytes, are recently reviewed as important co-factors in pancreas pathology [2]. Adipose tissue may exert a critical activity on cancerogenesis and, interestingly, even adipose tissue derived stem cells (ADSCs) may promote pancreatic cancer [3]. Cell differentiation in pancreatic cancer might involve therefore adipose tissue and factors released by adipocytes should play a fundamental role both in cancer onset and in its progression. Among these molecules, a great interest has been devoted quite recently to the hormonal role exerted by vitamin D_3 in pancreatic cancer, particularly its active 1,25 dihydroxylated form. The vitamin D_3 signaling, through its nuclear receptor, is de-regulated in pancreas cancer [4], an evidence that should mean that the role of vitamin D in cancer is essentially chemopreventive. The anti-inflammatory property of vitamin D has been shown also for tumors, where vitamin D decìficiency has been associated with cancer frequency and malignancy, although vitamin D dietary supplementation did not ameliorate the picture [5], while the expression of vitamin D receptor (VDR) in cancer cells has a prognostic positive meaning for pancreas adenocarcinoma [6]. Despite the wide bulk of evidence reporting the chemopreventive role of vitamin D, the mechanism by which active vitamin D_3 is able to counteract cancer progression and malignancy is yet far to be elucidated. The immune model, by which the active form of vitamin D_3, i.e. calcitriol, acts against cancer, includes the promotion of natural killer (NK) cells through the downregulation of the microRNAs miR-302c and miR-520c and subsequent up-regulation of the NKG2D ligands MICA/B and ULBP2 [7], activation of mast cells [8], induction of pro-inflammatry M1 macrophages [9]. Furthermore, vitamin D regulates a wide panoply of genes involved in cancer onset and progression. In breast cancer, for example, genes targeted by vitamin D are involved in innate immunity (CD14), cell and tissue differentiation (BMP6), extracellular matrix remodeling (Plau) and cell survival (Birc3) [10]. In this perspective, calcitriol may act directly by modulating the epithelial/mesenchymal transition (EMT) mechanism characterizing many forms of tumor, particularly pancreatic cancer.

1α,25(OH)$_2$vit D_3 in cancer progression and metastasis

Vitamin D has been recently associated to transition mechanism from muscle to adipose tissue. Treatment of myoblasts with oleic acid and thiazolidindiones causes conversion to adipocytes, according to a mechanism involving peroxisome proliferator-activated receptor-gamma (PPARγ) and CCAAT-enhancer-binding protein-alpha (C/EBP-α) and in this mechanism 1α,25(OH)$_2$vit D_3 or calcitriol should play a major role by modulating C/EBP-α and PPAR-γ expression through the vitamin D receptor (VDR)-dependent activity [11]. Experiments with C2C12 muscle cell line showed that calcitriol exerted a dose-dependent effect on the

transdifferentiation of muscle cells into adipocytes [12]. This evidence would suggest for a role of calcitriol also in epithelia-mesenchymal transition (EMT). EMT should play a major role in pancreas tumors, particularly in pancreatic ductal adenocarcinoma (PDAC), where the VDR-mediated signaling pathway may be involved in EMT regulation [13]. Models to speculate some activity ruled by vitamin D and VDR in tunor progression, fibrosis and EMT, sprout from evidence published elsewhere in the litarature.

Vitamin D appears to be a negative regulator of EMT and tissue remodelling. Particularly, in human bronchial epithelial cells (BEAS-2B), calcitriol inhibited both migration and invasion induced by TGF-ß1 and TGF-ß2 and the regulatory action of calcitriol appeared more effective to TGF-ß1-induced changes [14]. White adipose tissue (WAT) may trans-differentiate into fibroblast-like cells, particularly in some tumors such as breast cancer. Usually in many carcinomas such as breast, stomach, colon and pancreas cancers, tumoral cells support the expansion of molecular and cellular stroma in a mechanism known as “desmoplasia”, which has been reported as a strong fibrotic response. Particularly for breast cancer, where stroma is mainly composed by adipose tissue, the mechanism presumably occurs at the expense of adipocytes, generating a tumoral fibrous structure rich in fibroblast-like cells [15]. In this mechanism, a fundamental role may be exerted by the wingless and integrated-1 (Wnt)/β-catenin signalling pathway [16-19]. Wnt5a, a member of the Wnt-Frizzled pathway, is principally involved in the activation of the so called non canonical Wnt signaling, where Ror2, a member of the Ror-family receptor tyrosine kinases, should act as a receptor or coreceptor for Wnt5a. The Wnt5a-Ror2 axis is constitutively activated in cancer cells, to which it confers highly motile and invasive properties, mainly through the expression of matrix metalloproteinase genes, such as metalloproteinase 11 but also exhibiting a tumor suppressive action, particularly in breast and colorectal carcinomas [20]. The VDR-mediated inhibitory activity of EMT, exerted by calcitriol, may involve also Wnt signaling in tissue remodelling, tumor progression and organogenesis. A relationship between Wnt5a and vitamin D has been reported for endochondral ossification, where Wnt5a modulated a calcium-dependent mechanism via intracellular calcium release and activated PKC and CaMKII, while silencing VDR-signalling resulted in the Wnt5a-mediated PKC activity [21]. Interestingly, Wnt5a showed a bimodal (biphasicc) effect on the calcitriol-induced PKC effect, as low doses of Wnt5a caused a marked effect while higher doses (> 50 ng/ml) dampened PKC activation by calcitriol and this mechanism should involve also Ror-mediated signaling [21]. This model strongly suggests that calcitriol and Wnt5a should finely mediate their actions through similar receptor components and inter-relating pathways. Therefore, question raised if possible shared mechanisms may interplay the role of vitamin D in Wnt-mediated trans-differentiation in carcinomas.

Current evidence should support the idea that vitamin D plays a major role in cancer immunity and biology. Recent investigation suggests that vitamin D deficiency is associated with increased tumorigenesis, particularly in gastro-intestinal cancers [22]. In this context, the role of VDR-mediated signaling appeared as a fundamental hallmark in cancer onset and progression. Sherman.et al., showed that that VDR activation may reprogram reactive stroma in a tumor immune micro-environment to a less inflammatory, quiescent state, where the activity is associated with increased drug retention, cancer-immune response and even survival in pancreatic cancer [23,24]. The apparent chemo-preventive activity of vitamin D on pancreas cancer yet needs further elucidation. Pancreatic ductal adenocarcinoma (PDA) has a poor clinical outcome and activated pancreatic stellate cells (PSCs) should drive the severe stromal reactions leading to PDA [25-28]. Recent findings assessed the role of nutritional vitamin D, as its deficiency is associated to an advanced stage of pancreatic cancer [29]. Therefore, vitamin D_3 in cancer staging and progression, should play a major role, although much of the underlying mechanism yet remain obscure. Usually, these pancreatic diseases de-regulate vitamin D signaling, by increasing the expression of VDR and 24-hydroxylases (such as CYP24A1) and inhibiting the calcium sensing receptor (CaSR) involved in calcitriol activity [4]. Despite this report, there is no evidence about the benefit of vitamin D supplementation in pancreatic cancer [30]. Vitamin D should exert an anti-neoplastic role in several investigated carcinomas, but its mechanism of action still needs to be elucidated. The chemopreventive potential of vitamin D_3 might be related to a wide panoply of effects mediated by calcitriol, e.g. its action of cell trans-

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differentiation or the controversial role in immune tolerance. The analog of vitamin D, MART-10 (19-nor-2α-(3-hydroxypropyl)-1α,25$(OH)_2D_3$) exerts a potent anti-proliferative effect on PDA and both 1α,25$(OH)_2$vitD_3 and MART-10 decreased MMP-2 and MMP-9 secretion in BxPC-3 cancer cells, suggesting a role as potential anti-metastatic molecules [31]. Moreover, at least in breast cancer, the expression of VDR negatively co-related with cancer metastasis and with the pro-metastatic effect of tumor associated macrophages (TAMs) and the overexpression of VDR inhibited the epithelial-mesencymal transition (EMT) by decreasing E-cadherin (CDH1) and increasing α-smooth muscle protein (α-SMA) [32]. This evidence should enforce the role exerted by calcitriol as an anti-inflammatory molecule [33-35] and that the pleiotropic action of calcitriol in cancer may involve further mechanisms beside EMT, cancer progression and immunity [36]. Pro-inflammatory activity in cancer milieu inhibits the calcitriol anti-inflammatory action [37]. Therefore, taken together, the whole bulk of this reported evidence clearly supports the role of calcitriol as a chemo-preventive molecule acting on several mechanisms controlling cancer immunity and progression. Further insights are needed to comprehend how calcitriol exerts this property in cancers.

The trans-differentiation mechanism in cancer and vitamin D_3

The role of calcitriol in EMT and cancer has been recently addressed in a paper where colorectal cell lines DLD-1 and HCT116 treated with 1α,25$(OH)_2$vitD_3 were more sensitive to radiation than SW620 cell line with a high baseline mesenchymal feature; calcitriol exerted its best activity on tumor lines expressing high levels of E-cadherin and low levels of vimentin and EMT-related genes, such as *Snail/Slug* [38]. Actually, vitamin D should play a major role in cancer stem cells (CSC) [39]. From a molecular point of view, past reports have outlined the role of calcitriol in cell growth through a tumor growth factor beta (TGF-β) inhibition [40]. This activity may shed a light on the role attributed to calcitriol in modulating the adipocyte/fibroblast-like trans-differentiation observed in some tumors and hence in pancreatic cancer. Factors released by pancreas cancer lines, such as MiaPaCa, might induce adipocytes to change to a fibroblast-like phenotype and in this mechanism calcitriol should exert an inhibitory activity. In this respect, calcitriol might play a role either in modulating adipocyte action on tumor or promoting tumor activity towards cancer-associated adipose tissue. *In vitro* studies showed that adipocyte-released leptin inhibited cell growth of pancreas cell lines PANC-1 and MiaPaCa [41]. At least in mouse adipose tissue, from which *in vitro* trans-differentiation adipocyte/fibroblast-like cell in co-cultured 3T3-L1 and cancer cells systems was reported [42], calcitriol upregulates leptin from adipocyte [43]. Interestingly, leptin can induce metastasis, at least as reported in some tissue models of tumors, such as lung cancer. Adipose-tissue derived leptin promoted EMT transition and cell metastasis and induced TGF-β expression in A549 lung cancer cells [44]. In this perspective, suggestion arises if calcitriol inducing leptin may promote cancerogenesis, most probably vitamin D_3 might promote EMT in carcinomas through a leptin-mediated route. This evidence may fundamentally hamper a full comprehension of the role of calcitriol in cancer prevention and therapy. A possible solution should be earned by considering the complex network of interactions led by calcitriol both as an immune mediator (cytokine-like molecule) and an hormone. Furthermore, adipocytes can produce and release both calcidiol (25(OH)vitD_3) and calcitriol (1α,25$(OH)_2$vitD_3) [33] and hence the role of tumor-related adipose tissue through a calcitriol/VDR signaling should deserve particular attention. A focus onto the adipocyte/fibroblast-like transdifferentiation observed in cancer, particularly in carcinomas, may involve calcitriol, and more generally the biological homeostasis of vitamin D, in the complex mechanism leading to the peritumoral fibrosis response from white adipose tissue (WAT). The main pro-fibrotic and EMT-related factor, namely Wnt5a, is also an inflammation-related molecule released by adipocytes during metabolic syndrome (insulin resistance, obesity, type 2 diabetes) [45]. In prostate cancer the overexpression of hypoxia-inducible factor-1alpha (HIF-1α) induces EMT through the canonical Wnt/β-catetin pathway [46]. In colon carcinoma, HIFs play a complex role in the maintenance of tumor stemness and malignancy though an involvement of canonical Wnt signaling [47]. In addition, although the evidence was reported for osteoarthritis-derived osteoblasts, hypoxia via the HIF modulation triggered leptin production under vitamin D_3 stimulation while the Wnt/β-catenin agonist/antagonist dickkopf-related protein 2 (DKK2) was principally regulated by calcitriol

only [48]. If this mechanism should be shown in cancer cells or in the WAT/cancer micro-environment, the activity of calcitriol on EMT and cancer progression might be related to at least two different pathways, one of which including leptin. It has not yet been demonstrated, therefore, how calcitriol may exert its chemo-preventive action on epithelial tumors, even by inhibiting EMT transformation, malignancy and metastasis, if directly inibiting Wnt/β-catenin signaling or interacting with the HIF/leptin axis. In pancreatic cancer, both over-expression of HIF-1α and hypoxic conditions, induced the expression of the leptin receptor [49]. HIF-1α regulates migration of pancreatic ductal adenocarcinoma (PDA) cells through the up-regulation of the chemokine receptor CX3CR1 [50], which, at least in $CX3CR1^{pos}$ monocytes, is positively induced by calcitriol [51]. Therefore, a possible hypothesis on the HIF-1α/CX3CR1 axis in pacreatic cancer, is that PDA cells express CX3CR1, usually up-regulated by calcitriol induced macrophages, probably to escape to immune surveillance and response. Still, leptin is clearly involved in fibrosis, for example in cardiac muscle, kidney and liver [52-54]. In lung, leptin actively participates in the epithelial-mesenchymal cross talk, as the orexin, which is secreted by lipofibroblasts, binds to the its receptor on alveolar type 2 cells, and regulates the relationship between the parathyroid hormone-related protein (PHRP) and its receptor, whose failure may lead to a transdifferentiation lipofibroblast-myofibroblast, causing lung fibrosis [55]. Leptin, which is a downstream target of PHRP receptor, may downregulate the latter [55]. Lung model of leptin biology in the lipofibroblast/myofibroblast transition, might shed a light on the possible role exerted by leptin or other adipocyte-derived hormones, such as vitamin D_3, in WAT/cancer related fibrosis. Fibrotic shell may ensure cancer to better hold out against immune response and therapy.

Calcitriol has been shown to inhibit subepithelial fibrosis [14] and in heart calcitriol reduced expression of profibrotic TGF-β1 and the accumulation of collagens I and III [56]. This inhibitory activity by calcitriol towards fibrosis might lead to the conclusion that the vitamin should play a dramatic role in the epithelial/mesenchymal transition depending on VDR expression, which in turn depends on different cell types and different immune microenvironment (pro- or anti-inflammatory/tolerant milieu).

Conclusions

The role of calcitriol in cancer progression and metastasis, as well as in EMT, is still far to be completely understood. According to the many results reported in literature, it might simply depend on the gain/loss of VDR expression and signaling in cancer cells. In addition, calcitriol upregulation of VDR in tolerant lymphocytes should avoid cancer to be faced by immune surveillance and succesfull response. In the absence, failure or downregulation of VDR, calcitriol might exert a potent induction of leptin, particularly from tumor surrounding/neighborough WAT, leading to adipocyte EMT and fibrosis, maybe through a Wnt5a-mediated mechanism. This might explain why vitamin D supplementation in cancer therapy has not reached any promising effect.

The nutritional status of vitamin D, however, represents a big concern for cancer onset and development, particularly if associated with high metabolic risk factors, such as saturated/unsaturated lipid rich diets and critical lifestyles including smoking, lack in calorie restriction, scarce frequency in muscular exercise, genetic background for metabolic syndrome and so on. Many further insights are needed and the many workshops aiming at expanding the debate worldwide, may give a cleared elucidation of the role of calcitriol in panreatic cancer in the next future [57].

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